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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Mitchell et al.

Art Unit: 1614

Application No. 09/424,519

Examiner: B. Y. S. Kwon

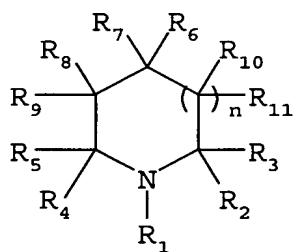
Filed: March 3, 2000

For: THE USE OF A NITROXIDE OR A
PRODRUG THEREOF IN THE
PROPHYLACTIC AND THERAPEUTIC
TREATMENT OF CANCER

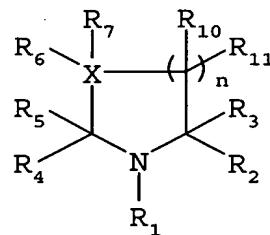
**AMENDMENTS TO CLAIMS MADE IN
RESPONSE TO OFFICE ACTION DATED SEPTEMBER 18, 2002**

*(Deletions are indicated by brackets,
while insertions are indicated by underlining)*

1. (Amended) A method for the [prophylactic or] therapeutic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer due to a genetic defect in the abl, bcl2 or p53 gene a nitroxide or a prodrug thereof in an amount sufficient to [prevent or] treat said cancer, wherein said cancer is susceptible to [prevention or] treatment by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I



Formula II

wherein R₁ is selected from the group consisting of H, OH, OZ, O·, =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O· or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic

group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein,
wherein R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a C₁₋₂₀
alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R"]_m-CH₃, wherein
R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R" is
selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic
group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein,
m < 30, and R₂ and R₃ or R₄ and R₅ can be connected through one or more members,
each of which is independently selected from the group consisting of carbon and a
heteroatom, wherein R₆, R₇, R₈ and R₉ are independently selected from the group consisting
of hydrogen, a hydroxyl group, a C₁₋₂₀ aldehydic group, a C₁₋₂₀ keto group, a primary amino
group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a
sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a
sulfamato group, a metal-containing group, a silicone group, a halide, a C₁₋₂₀ ester-containing
group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a
phosphonato group, a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -
CH₂-[CR' R"]_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀
aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic
aromatic group, and R" is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic
group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group,
a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid
and a protein, and m < 30, and wherein any one of R₆, R₇, R₈ and R₉ can be attached
covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I,
one of R₆ and R₇ and one of R₈ and R₉ can be absent such that a double bond joins the two
carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I,
and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R₁₀ and R₁₁ are
independently selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀
aliphatic/aromatic group, a heteroatomic group, a C₁₋₂₀ ether-containing group, a C₁₋₂₀ keto
group, a C₁₋₂₀ aldehydic group, a carboxamido group, a cyano group, an amino group, a

carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R₁₀ and R₁₁ can be connected through an aliphatic group and/or an aromatic group, or R₁₀ and/or R₁₁ can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

2. (Canceled)

3. (Canceled)

4. (Amended) The method of claim [3] 1, wherein said aliphatic group is branched, substituted and/or unsaturated.

6. (Amended) The method of claim [3] 1, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

8. (Amended) The method of claim [3] 1, wherein the metal of said metal-containing group is selected from the group consisting of a transition metal and a lanthanide.

12. (Amended) The method of claim [3] 1, wherein said alicyclic group is substituted and/or unsaturated.

14. (Amended) The method of claim [3] 1, wherein said amino group is substituted.

21. (Amended) The method of claim [3] 1, wherein said noncarbon/nonoxygen moiety is selected from the group consisting of boron, sulfur, nitrogen and phosphorus.

22. (Canceled)

23. (Amended) The method of claim [22] 1, wherein said [tumor suppressor gene] genetic defect is the p53 gene.

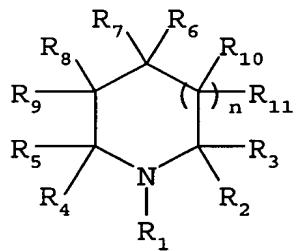
24. (Canceled)

25. (Canceled)

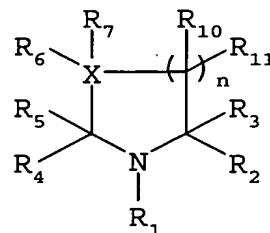
26. (Canceled)

27. (Canceled)

28. (New) A method for the prophylactic or therapeutic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer due to an inherited genetic defect selected from the group consisting of ataxia telangiectasia, Cowden's disease, Torre's syndrome, Gardner's syndrome, Wiskott-Aldrich syndrome, Peutz-Jeghers syndrome, Bloom's syndrome, Fanconi's syndrome, Wemers syndrome, Chediak-Higashi syndrome, retinoblastoma, Beckwith-Wiedeman syndrome, and neuroblastoma, a nitroxide or a prodrug thereof in an amount sufficient to prevent or treat said cancer, wherein said cancer is susceptible to prevention or treatment by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I



or

Formula II

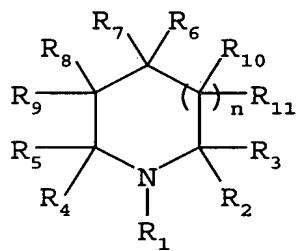
wherein R₁ is selected from the group consisting of H, OH, OZ, O·, =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O· or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic

group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein,
wherein R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a C₁₋₂₀
alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R"]_m-CH₃, wherein
R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R" is
selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic
group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein,
m < 30, and R₂ and R₃ or R₄ and R₅ can be connected through one or more members,
each of which is independently selected from the group consisting of carbon and a
heteroatom, wherein R₆, R₇, R₈ and R₉ are independently selected from the group consisting
of hydrogen, a hydroxyl group, a C₁₋₂₀ aldehydic group, a C₁₋₂₀ keto group, a primary amino
group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a
sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a
sulfamato group, a metal-containing group, a silicone group, a halide, a C₁₋₂₀ ester-containing
group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a
phosphonato group, a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -
CH₂-[CR' R"]_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀
aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic
aromatic group, and R" is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic
group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group,
a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid
and a protein, and m < 30, and wherein any one of R₆, R₇, R₈ and R₉ can be attached
covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I,
one of R₆ and R₇ and one of R₈ and R₉ can be absent such that a double bond joins the two
carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I,
and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R₁₀ and R₁₁ are
independently selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀
aliphatic/aromatic group, a heteroatomic group, a C₁₋₂₀ ether-containing group, a C₁₋₂₀ keto
group, a C₁₋₂₀ aldehydic group, a carboxamido group, a cyano group, an amino group, a

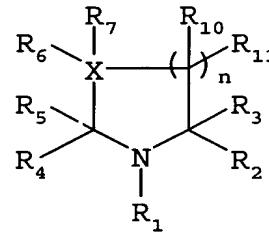
carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato group, a sulfinato group, and a sulfonato group, and wherein R₁₀ and R₁₁ can be connected through an aliphatic group and/or an aromatic group, or R₁₀ and/or R₁₁ can comprise a member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a protein.

29. (New) The method of claim 28, wherein the inherited genetic defect is ataxia telangiectasia.

30. (New) A method for the prophylactic treatment of cancer in an animal, which method comprises administering to an animal at risk for developing a cancer or having a cancer a nitroxide or a prodrug thereof in an amount sufficient to prevent said cancer, wherein said cancer is susceptible to prevention by said nitroxide or prodrug thereof, and wherein said nitroxide or prodrug thereof is a compound of Formula I or II:



Formula I



or

Formula II

wherein R₁ is selected from the group consisting of H, OH, OZ, O·, =O and Y, wherein Y is a leaving group, which can be converted to H, OH, O· or =O by reaction with a nucleophilic agent, and Z is selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid and a protein, wherein R₂, R₃, R₄ and R₅ are independently selected from the group consisting of a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -CH₂-[CR' R"]_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic aromatic group, and R" is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic group, a monocyclic

aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid, and a protein,
m ≤ 30, and R₂ and R₃ or R₄ and R₅ can be connected through one or more members,
each of which is independently selected from the group consisting of carbon and a
heteroatom, wherein R₆, R₇, R₈ and R₉ are independently selected from the group consisting
of hydrogen, a hydroxyl group, a C₁₋₂₀ aldehydic group, a C₁₋₂₀ keto group, a primary amino
group, a secondary amino group, a tertiary amino group, a sulfido group, a disulfido group, a
sulfato group, a sulfito group, a sulfonato group, a sulfinato group, a sulfenato group, a
sulfamato group, a metal-containing group, a silicone group, a halide, a C₁₋₂₀ ester-containing
group, a carboxyl group, a phosphato group, a phosphino group, a phosphinato group, a
phosphonato group, a C₁₋₂₀ alkyl group, a C₂₋₂₀ alkenyl group, a C₂₋₂₀ alkynyl group, and -
CH₂-[CR' R'']_m-CH₃, wherein R' is selected from the group consisting of hydrogen, a C₁₋₂₀
aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, and a multicyclic
aromatic group, and R'' is selected from the group consisting of hydrogen, a C₁₋₂₀ aliphatic
group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group,
a C₁₋₂₀ alicyclic group, a noncarbon/nonoxygen moiety, a carbohydrate, a lipid, a nucleic acid
and a protein, and m ≤ 30, and wherein any one of R₆, R₇, R₈ and R₉ can be attached
covalently or noncovalently to a polymer of synthetic or natural origin, wherein in Formula I,
one of R₆ and R₇ and one of R₈ and R₉ can be absent such that a double bond joins the two
carbon atoms to which the remaining R groups are attached, wherein n = 0-20 in Formula I,
and n = 1-20 in Formula II, wherein X is a heteroatom, and wherein R₁₀ and R₁₁ are
independently selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic
aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, a C₁₋₂₀
aliphatic/aromatic group, a heteroatomic group, a C₁₋₂₀ ether-containing group, a C₁₋₂₀ keto
group, a C₁₋₂₀ aldehydic group, a carboxamido group, a cyano group, an amino group, a
carboxyl group, a selenium-containing group, a sulfato group, a sulfito group, a sulfenato
group, a sulfinato group, and a sulfonato group, and wherein R₁₀ and R₁₁ can be connected
through an aliphatic group and/or an aromatic group, or R₁₀ and/or R₁₁ can comprise a
member selected from the group consisting of a carbohydrate, a lipid, a nucleic acid and a
protein.

31. (New) The method of claim 30, wherein said aliphatic group is branched, substituted and/or unsaturated.

32. (New) The method of claim 31, wherein said aliphatic group is substituted with a member selected from the group consisting of oxygen, phosphorus, selenium, sulfur and nitrogen.

33. (New) The method of claim 30, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

34. (New) The method of claim 33, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

35. (New) The method of claim 30, wherein the metal of said metal-containing group is selected from the group consisting of a transition metal and a lanthanide.

36. (New) The method of claim 33, wherein said aromatic group is substituted.

37. (New) The method of claim 36, wherein said aromatic group is substituted with a heteroatom.

38. (New) The method of claim 37, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

39. (New) The method of claim 30, wherein said alicyclic group is substituted and/or unsaturated.

40. (New) The method of claim 38, wherein said alicyclic group is substituted with a heteroatom.

41. (New) The method of claim 30, wherein said amino group is substituted.

42. (New) The method of claim 41, wherein said amino group is substituted with up to three substituents selected from the group consisting of a C₁₋₂₀ aliphatic group, a monocyclic aromatic group, a bicyclic aromatic group, a multicyclic aromatic group, and a C₁₋₂₀ alicyclic group.

43. (New) The method of claim 42, wherein said aromatic group comprises a five- or six-membered ring, in which each of the five or six members is independently selected from the group consisting of carbon and a heteroatom.

44. (New) The method of claim 43, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

45. (New) The method of claim 42, wherein said aromatic group is substituted.

46. (New) The method of claim 45, wherein said aromatic group is substituted with a heteroatom.

47. (New) The method of claim 46, wherein said heteroatom is selected from the group consisting of nitrogen, oxygen, sulfur, phosphorus and boron.

48. (New) The method of claim 30, wherein said noncarbon/nonoxygen moiety is selected from the group consisting of boron, sulfur, nitrogen and phosphorus.

49. (New) The method of claim 30, wherein the cancer is caused by a genetic defect selected from the group consisting of the abl, bcl2 or p53 gene.